Naloxone
Expanded Access: OTC status
Considerations for a Nonprescription Drug Development Program

Andrea Leonard-Segal, M.D., M.S.
Director, Division of Nonprescription Clinical Evaluation

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Regulatory Requirements for Nonprescription Drug Marketing

Durham Humphrey Amendment to the Food, Drug and Cosmetic Act (1951)

- **Formally differentiates Rx from Non Rx Drugs**
- 2 Criteria carve niche for Prescription Drugs:
  - Drug can be used safely only under supervision because of:
    - drug's toxicity or
    - other potentiality for harmful effect, or
    - method of its use, or
    - collateral measures necessary to its use
  - If drug is limited by an approved application to use under professional supervision
- Otherwise, the drug should be available without a prescription.
- Code of Federal Regulations (21 CFR 310.200) describes the procedure by which drugs that have been limited to prescription use shall be exempted from prescription-dispensing requirements

How Can Drugs Be Marketed in the U.S.?

- There are two marketing options for drugs in the U.S.
  - Prescription (Rx)
  - Nonprescription = Over-the-Counter (OTC)

- Behind-the-Counter is not a marketing venue in the U.S.
  - Available in European and other international markets
    - Intermediate distribution status for drugs that allows trained pharmacists to interact with a consumer and then select and provide medication to the consumer
    - No input from a physician required

How Can Drugs Be Marketed in the U.S.?

- Law has been interpreted so dual marketing of the same active ingredient in products that are both Rx and OTC can only occur when a clinically meaningful difference exists between the two that makes the Rx product safe only under the supervision of a licensed practitioner
  - A drug cannot be marketed both Rx and OTC for the same indication, population, and same conditions of use

How Might the Law Apply to Naloxone?

- Would a clinically meaningful difference exist between an OTC naloxone and Rx naloxone so the current Rx product(s) would remain after the OTC switch?
- Would a difference in dosage form between the Rx products and the proposed OTC product be interpreted as a clinically meaningful difference?

OTC Drug Labeling

OTC "Drug Facts" Label

- OTC drugs have their own labeling regulations (21 CFR 201.66)
- Standardized format is intended to provide clarity and consistency to consumers so they know what to expect from OTC labels and where to find the important information
- Limited "real estate" on an OTC product
- All important information necessary for effective and safe use of OTC product must be in the Drug Facts Label
  - This would be the case for naloxone

Drug Facts
Active ingredient(s) ***Purpose***
Use(s)
Warnings
Do not use
Ask a doctor before use if you have
Ask a doctor or pharmacist before use if you are
When using this product
Stop use and ask a doctor if
If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.
Directions
Other information
Inactive ingredients
Questions or comments?

Consumer Information Leaflet (CIL)

- This additional labeling element sometimes is included inside the box of an OTC drug product
  - May provide additional information about the drug or the condition the drug treats that can be useful to the consumer
  - May provide explicit diagrams on how to use the product
  - Naloxone products could have CILs

How Could Naloxone Become an OTC Drug?

Regulatory Mechanisms by which Naloxone Could Become an OTC Drug

- New Drug Application (takes months, proprietary, product specific, applicant pays user fee)
- Rulemaking (takes years, public, ingredient specific, no user fee)
  - Regulated under the OTC Drug Monograph

New Drug Application for OTC Marketing

Proprietary

Each Switch NDA→ Fresh Look at the Drug
All components of Rx NDA and more….

- Chemistry
  - New formulation, stability, packaging, etc.
- Pharmacology/Toxicology
  - New formulation, new method of delivery, new combination of ingredients, possibility of longer duration of exposure in the OTC venue because of repeated use, etc.
- Microbiology (if applicable)
  - e.g., Drug resistance issues raised by the OTC setting, sterility issues
- Clinical Pharmacology
  - New formulation, new combination, etc.

Each Switch NDA→ Fresh Look at the Drug
All components of Rx NDA and more….

- Efficacy data
  - If OTC and Rx indications differ, if ↓dose, if not bioequivalent to approved reference drug, etc.
- Safety data
  - Clinical trials
  - Postmarketing worldwide safety data to identify new signals after broad time and extent of Rx product use and to assess safety in markets in which this product may already be nonprescription (e.g., Sweden)
- Consumer studies (unique to OTC drug evaluation)
  - New OTC indication, new warnings, new directions for use, etc.
- Labeling
- An OTC application for Naloxone, depending upon the formulation, may need to contain new data to address all of these components.

Additional Words on Efficacy and Safety Data

- Data from Rx NDA can sometimes support the switch…sometimes need additional data
  - Naloxone
    - Efficacy
      - Switch of approved Rx product – no efficacy data needed
      - New naloxone formulation may need new efficacy data based on differences in clinical pharmacology profile compared with that of the approved reference drug
    - Safety
      - Switch of approved Rx product supported by current safety database (clinical studies and postmarketing)
      - New formulation
        - » New clinical safety data needed (topical formulation)
        - » If more bioavailable than the reference drug, wise to market Rx first to acquire postmarketing safety database before marketing OTC

Post-Marketing Safety Data for OTC Switch

- Sources
  - Adverse Event Reporting System
  - WHO International Drug Monitoring Program
  - Literature review
  - Drug abuse and overdose data
    - For Naloxone, need to understand the potential for conversion into an opioid agonist that could be abused

Consumer Studies Unique to OTC Drug Assessment

- Conducted to support safe and effective use in the OTC setting
  - Label Comprehension
  - Human Factor
  - Self-Selection
  - Actual Use

Consumer Studies Are Helpful When…..

- Drug is first in its class to OTC market
- New OTC target population
- New OTC indication
- Substantive labeling change to existing OTC product
- New directions for use (not previously seen in the OTC marketplace)

Needed to support a Naloxone Switch

Label Comprehension Study

- First step in predicting Consumer Behavior
  - Can the consumer understand the label?
    - If not, likely will not use the product properly
    - However, converse is not necessarily true
- Tests if label communicates messages key to proper drug use
  - Consumer reads the label and responds to questions about it
  - Not a clinical trial……No drug administered

Human Factors Study

- Can assess whether prospective consumers can follow the steps outlined in the directions for use to properly prepare or measure a product for dosing
  - Not always needed for an NDA
  - Can help to improve complex dosing instructions
- Naloxone
  - e.g., Could assess if consumers can properly prepare or use product syringe based upon the directions

Self-Selection Study

- Tests whether, based on reading the product label, consumers can properly select to use or not to use the product
  - Can consumers self-diagnose the condition for which the drug is indicated?
  - Can they recognize whether the drug would be appropriate for them to use based upon their personal medical history?
  - No drug administered

Self-Selection and Naloxone

- For Naloxone, the individual administering drug would not be the person receiving it
  - This OTC paradigm exists now: parents "self-select" to treat symptomatic conditions in their minor children
  - Data will be needed to assess whether the individual administering naloxone could properly diagnose the opioid overdose and determine that it is appropriate to give naloxone based upon the information on the Drug Facts Label

Actual Use Study (an "atypical" clinical trial)

- Provides data to enable us to predict if a drug will be used properly and safely in the OTC setting.
- Simulates OTC use of product "naturalistic setting"
  - Generally open-label
  - Access to study medication simulates what would occur if the drug were approved OTC
  - Limited study investigator contact
    - Timing of follow-up contacts consumer driven (as much as possible)
- Actual Use Data would be needed to support an OTC application for Naloxone

Rulemaking to Bring Naloxone into the OTC Drug Monogaph

Public Process

Rulemaking Options to Bring Naloxone OTC

- FDA could initiate rulemaking on its own or in response to a Citizen Petition requesting that FDA do this
- Data needed would be the same as for the NDA
- Process involves data review, multiple Federal Register publications soliciting comments, comment review
- Ultimately final rule would state that naloxone (active ingredient) is or is not Generally Recognized as Safe and Effective OTC to treat opioid overdose when administered as a particular type of formulation

Some Other Issues Raised by OTC Naloxone

- Needle safety for the injectable formulation
- The impact of the injectable no longer being a prescription drug
- Management of withdrawal reactions
- Would it encourage opioid misuse or adversely impact the use of 911
- Educational campaigns
- FDA does not control OTC drug advertising; FTC does

Summary

- There are different regulatory pathways to consider for the Rx to OTC switch of naloxone
- There are many interesting regulatory and scientific issues to address to support the expanded access of naloxone via OTC marketing
- Consumer data (among other data) would be essential to support a naloxone switch

The End

Time and Extent Application Process

- Process outlined in the Code of Federal Regulations (21 CFR 330.14)
- The data to support a TEA are the same as would be needed to support an NDA
- Once listed in the monograph, the active ingredient can be used if it meets the conditions of use as specified therein
- Guidance on TEAs located at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078902.pdf